Elevated Serum Levels of Interleukin-2 Soluble Receptor in Patients with Rheumatoid Arthritis

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Abstract

Background: Rheumatoid arthritis (RA) is a multifactorial autoimmune disease with unidentified etiology. We hypothesized that T cell activation in the rheumatoid synovium might be responsible for the induction of increased expression of soluble interleukin 2 receptor (sIL2R).

Objectives: To evaluate in RA whether T cell activation, as reflected by levels of sIL2R, was associated with the disease outcome.

Materials and methods: Serum levels of sIL2R were measured in 69 untreated patients with different stages of RA (48 women and 21 men, aged 53.76±14.2 years, age range 45-60, mean of arthritis duration 12.4±7.6 years) and 22 healthy subjects (17 women and 5 men, aged 34.9±7.7 years, age range 27-54). All patients fulfilled the American College of Rheumatology criteria for RA. RA patients were classified by the severity of disease (mild, moderate or severe). Levels of serum sIL2R were measured by use of ELISA. A Student’s t test was used to analyze the differences between the groups. The Pearson correlation was performed to determine the association of sIL2R and the severity of RA disease.

Results: Serum sIL2R levels were significantly elevated as compared to those of the control group (p=0.001). The mean value of sIL2R in RA patients was 2077±278 pg/mL (range 1093 to 2820 pg/mL) and that of controls was 683±126 pg/mL (range 266 to 800 pg/mL); p<0.001. In addition, a significant correlation between serum sIL2R and severity of RA was observed (r=0.673; p<0.001)

Conclusion: A significant correlation between serum sIL2R and RA severity exists that may aid evaluation of the clinical outcome and usefulness of the treatment of RA. Serum sIL2R levels increase due to disease activity and the amount of increase corresponds to the degree of inflammation.

Keywords: serum soluble interleukin 2 receptor (sIL2R), rheumatoid arthritis, disease outcome

Background

Rheumatoid arthritis (RA) is an autoimmune disease with 1% prevalence in the industrialized world. Rheumatoid arthritis is a chronic inflammatory disease leading to joint destruction. Rheumatoid arthritis is an inflammatory autoimmune disease that primarily attacks the synovial membrane of the minor joints leading to
joint stiffening, swelling, and loss of function in the joints. Identification of the role of T cells and their interaction with other cell types remains a major challenge to our understanding of the pathogenesis of RA [1].

Rheumatoid arthritis is a chronic, systemic inflammatory disorder that may affect many tissues and organs, but principally attacks flexible (synovial) joints. Over two decades, advances in our understanding of the pathogenesis of RA have translated directly into benefit for patients. Rheumatoid synovitis is characterized by an intense inflammatory infiltrate consisting primarily of activated lymphocytes. Activation of the immune system by an ongoing autoimmune disease is associated with measurable alterations in T-lymphocyte function [2].

Recent research has uncovered an important role of cytokines which promote inflammation. Since its discovery in 1985 the sIL2R has become a clinically valuable tool for several diseases. Soluble cytokine receptors regulate inflammatory and immune events by functioning as agonists or antagonists of cytokine signaling. Soluble IL2R is a circulating form of a membrane receptor localized on lymphoid cells. The biological function of sIL2R has not been completely understood. Substantially, it seems to reflect T lymphocyte activation in diseases of different pathology. Several lines of evidence indicate sIL2R measurements to be useful in determining disease progress and prognosis. The molecular mechanism of synovitis is associated with T cell activation and an elevated production of proinflammatory cytokines, metalloproteinases, and adhesion molecules [3,4].

Based on the essential pathogenic role of inflammation for progression of RA, we hypothesized that T cell activation in the rheumatoid synovium might be responsible for the induction of increased expression of sIL2R. Soluble IL2R is a reliable biomarker for disease activity in inflammatory disorders such as RA. Soluble IL2R is a surrogate marker of T-lymphocyte activation and proliferation [5].

Therefore, the aim of this study was to investigate the correlation between sIL2R with the degree of severity of RA, which may further imply for better understanding of the pathology of this disease.

Materials and methods

Serum IL2R levels were examined in 69 untreated patients with different stages of RA (48 women and 21 men, aged 53.76±14.2 years, age range 45-60, mean of arthritis duration 12.4±7.6 years) and 22 healthy subjects with no underlining diseases were also recruited to be a control group of the study (17 women and 5 men, aged 34.9±7.7 years, aged range 27-54). Pregnant women, patients with cancer, diabetes mellitus, autoimmune illnesses, hepatitis, or patients under dialysis were excluded from the study.

All active RA patients who agreed to be included into the project were classified into 3 groups by severity based on the Rheumatoid Arthritis Disease Activity Index (RADA1): Mild, score <10; Moderate, score 10-20; Severe, score>20. The classification of severity was made by a rheumatologist on presentation. Patients included in this study had not received biological immunomodulatory drugs.

The project had been approved by the Ethic Committee of the Clinical Center and written informed consents were obtained from all participants.

Five mL of blood samples were drawn and immediately chilled. Serum was separated by centrifugation at 4°C at 3000 rpm for 10 min. The specimens were kept at −20°C and analyzed within 2 weeks.

The production of sIL2R was measured by use of enzyme-linked immunosorbent assay (ELISA). Soluble IL2R concentrations (pg/mL) were expressed as the mean value (x)±standard deviation (SD). Student’s t test was used to analyze the differences between the groups. One-way ANOVA was initially performed to determine whether overall statistically significant differences existed before using the two-tailed paired or unpaired Student’s t test. The Pearson correlation was performed to determine the association of sIL2R and the severity of RA patients. The statistical significant difference was considered when p value was less than 0.05.

Results

This study was performed to determine the correlation of sIL2R and the degree of severity of RA disease.

Levels of sIL2R were elevated in the group of patients as compared to those of healthy subjects and correlated significantly with several parameters of clinical activity, including the functional capacity, joint score, visual-analogue score and C-reactive protein (CRP). C-reactive protein is another common test that measures disease activity. Positive serum CRP (CRP level >15mg/dL) was found in 61% of patients (p=0.024; r=0.711).

The mean value of sIL2R of the patients group was 2077±278 pg/mL (range 1093 to 2820 pg/mL) and that of controls was 683±126 pg/mL (range 266 to 800 pg/mL); p<0.001. Patients with RA vary considerably in terms of their clinical manifestations and outcome. The reason for these differences may be due to the severity of disease. T lymphocyte activation, as reflected in elevated sIL2R levels,
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is frequent in RA patients and is associated with more severe disease. There was a positive significant correlation between serum sIL2R concentrations and the RA severity (p<0.001; Pearson correlation coefficient r=0.673).

Our data supported the notion that T-cell activation plays a role in the immunopathologic processes leading to clinical RA. Soluble IL2R concentration in serum provides a reliable immunological marker to assess disease activity in RA. In RA, sIL2R concentrations are increased and are a potentially useful adjunct in monitoring disease activity.

Discussion

In the last decade we have significantly increased our knowledge of the underlying pathobiology of RA. Rheumatoid arthritis is a chronic, relapsing, inflammatory disease characterized by arthritis and systemic inflammation. The pathogenesis of RA is incompletely understood. It involves collaboration between dendritic cells, T cells, and monocytes/macrophages, which may initiate and perpetuate immune activation. Soluble IL2R appears in serum, concomitant with its increased expression on cells and correlates with increased activation of T cells. Soluble IL2R is secreted by lymphocytes upon activation and has been used as a marker of immune activation in several diseases. Soluble IL2R is part of a membrane receptor for IL2, which can be localized on the cell surface of different lymphoid cell lines including activated T and NK cells, monocytes, eosinophils. Activation of T-lymphocytes not only leads to the expression of IL2R molecules on the cell surface but also releases sIL2R molecules into the circulation. Soluble IL2R exists in three different forms: alpha (IL2Rα, CD25, previously Tac antigen, M=55 kd), beta (IL2Rβ, CD122, M=75 kd), and gamma chains (IL2Rγ, CD132, M=64 kd). Soluble IL2Rα appears to possess the best diagnostic value in a number of diseases associated with T-cell stimulation. One of the most interesting biological features of sIL2R is its ability to bind IL2 with an affinity similar to that of the form present on the cell surface. The elevated sIL2R levels may lead to a decreased cellular response to IL2. Support for a central role of T cells in RA pathogenesis comes from the demonstration that the strongest genetic risk for RA is conferred by the HLA locus 27. Serum sIL2R concentrations reflect lymphocyte activation in vivo [6,7].

The first event in RA is probably antigen-dependent activation of T cells. T cell activation and function are critically regulated by positive and negative costimulatory molecules. Aberrant expression and function of costimulatory molecules have been associated with persistent activation of self-reactive T cells in autoimmune diseases such as RA. The activation of T cells by as yet unknown antigens in the immunogenetically susceptible host is most probably the event that initiates the rheumatoid process [8-10].

Rheumatoid arthritis is characterised by the presence of activated lymphocytes in the synovial compartment, which are classically considered to be of particular importance to the pathogenesis of the disease. Soluble IL2R levels are considered to be a measure of in vivo T-lymphocyte activation and are elevated in the sera of many patients with inflammatory and immune-mediated diseases [11]. Studies suggest a correlation of serum IL2R levels with activity of autoimmune diseases such as RA. In human studies, an increase of sIL2R levels during this process has been noted, both in serum and in synovial fluid [12-15].

Soluble IL2R levels in the serum reflect activation of T lymphocytes in the periphery or in tissues. We have investigated the level of T cell activation in RA patients. T-cells are the dominant type of cell that infiltrates the synovial membrane in RA. A significant correlation was observed between serum sIL2R and RA severity. However, our work had several limitations. First, the blood sample from every patient was not collected at the same time of the day and this was a single point measurement. Second, there were several other factors which might have influence on sIL2R levels, for example, duration of RA [16,17].

Hence sIL2R measurement in serum may be helpful for qualifying patients to receive IL2 immunotherapy. Detailed clinical trials show that serum sIL2R levels are related to disease duration and a decline in sIL2R concentration may result from joint improvement. Some reports indicate relationships between sIL2R and laboratory markers of inflammation, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) [18,19].
RA patients were not treated before the study. Soluble IL2R measurements in serum give a better tool for the assessment of the immune system activity. Furthermore, the interactions of T cell function with inflammatory cells should be taken into account.

Conclusion

In this study, we examined the role of T lymphocytes in RA by the serum sIL2R levels as an indirect measure of T lymphocyte activation. RA patients have fundamental abnormalities in T cell function. Activation of T lymphocytes can be evaluated by measuring circulating levels of sIL2R. We have shown that activated lymphocytes are also found in the rheumatoid lymph nodes and peripheral blood, and that their proportions are increased in the acute phase of the disease. We suggested an important role of circulating activated lymphoid populations in the pathogenesis of RA. An increase of sIL2R levels during RA has been noted in serum. The significant correlation between serum sIL2R and RA severity that was found may aid the evaluation of disease severity and may be useful for the treatment of RA. These preliminary data show that serum sIL2R levels are often elevated in systemic vasculitis during clinical exacerbation suggesting that T-lymphocytes may be activated in the acute phase of the disease.

Conflict of interest: The authors who have taken part in this study declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

References